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243 CHARLES STREET

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STAFF

David G. Cogan, M.D.:	*Associate Professor of Ophthalmic Research — Director*
V. Everett Kinsey, Ph.D.:	*Assistant Professor of Ophthalmic Research*
Elek J. Ludvigh, Ph.D.:	*Associate in Ophthalmic Research*
W. Morton Grant, M.D.:	*Associate in Ophthalmic Research*
Charles W. Dyson, M.D.:	*Fellow in Ophthalmic Research*
Frederic C. Merriam, A.M.:	*Fellow in Ophthalmic Research*
Charles L. Schepens, M.D.:	*Fellow in Ophthalmic Research*
Robert R. Trotter, M.D.:	*Fellow in Ophthalmic Research*
Ernst Bárány, M.D.:	*Visiting investigator*
Pierre Danis, M.D.:	*Visiting investigator*

WITH its roots implanted both in the basic sciences and in clinical ophthalmology, the Howe Laboratory has continued its attempt to push forward, however so slightly, the frontier of knowledge pertaining to the ophthalmic sciences. The ultimate importance of these contributions can be properly assessed only with the passage of time; some will appear to grow in value and others to diminish. But it is, nevertheless, certain that the diversification of interests in the Howe Laboratory makes it a safe investment from the research point of view; success or failure of the Laboratory as a whole does not depend on the outcome of a single line of investigation.

Laboratory Sciences

The mechanism of aqueous humor formation has been further elucidated by the studies of Dr. Kinsey and Dr. Bárány. A method for determining the rate of flow of aqueous humor in individual animals under physiologic conditions was devised. In rabbits the rate of flow was found to be approximately 3 cu. mm. per minute. The importance of a knowledge of rate of flow comes from the fact that once this rate is known it is possible to draw conclusions concerning the means of entrance into the anterior chamber of any substance simply from a knowledge of the rate of disappearance of this substance and its relative concentration in the aqueous humor compared with that in the plasma under steady state (equilibrium) conditions. Both of these values are easily determined experimentally. Exact knowledge of the rate of flow has added quantitative proof to tentative conclusions drawn previously concerning the mode of entrance of the physiologically important substances — sodium, chloride, water and glucose. It appears that sodium, chloride and other electrolytes enter the anterior chamber by an energetic process (secretion), whereas water, glucose and other non-electrolytes enter not only by this means but also and predominantly from the iris by diffusion. All the constituents of the aqueous humor leave in part by a flow process, and the water and non-electrolytes also leave by diffusion. From this information it can be inferred that the intra-ocular pressure depends upon rate of secretion, resistance to flow and resistance to diffusion. Increased secretion, or increased resistance to flow tends to increase the pressure, whereas decreased secretion, or decreased resistance to flow or increased diffusion tends to lower the pressure.

Comparative studies of the concentration of chloride in the aqueous humor and plasma of rabbits, dogs, and human beings, using several methods of chemical analysis, have been completed. By the use of newer methods, it has been found that the relative concentration of chloride in the aqueous humor compared with that in the plasma at steady state is within the limits set by the Gibbs-Donnan equilibrium. The discrepancy between these results and those obtained previously in other laboratories is probably due to an error in the chemical methods that have been employed.

Analyses of the relative carbon dioxide of plasma and aqueous humor in rabbits have shown that there is a sufficient excess of bicarbonate in the aqueous humor to account for the excess osmotic pressure in this fluid compared with that in the plasma.

The first of a series of investigations on the chemistry of the cornea and lens has been undertaken by Dr. Kinsey and Mr. Frederic Merriam.* In the initial experiments, the lens is being maintained under *in vitro* conditions, and the synthesis of glutathione is being studied by means of tracer experiments involving radioactive labeled amino acids. Since the concentration of glutathione falls along with the formation of cataracts, information concerning possible synthesis of this compound is thought to be of importance. The results obtained thus far are technically promising, since lenses have been maintained *in vitro* for several days in their normally transparent condition.

Apparatus for measuring the osmotic pressure of ocular fluids has been set up in the Laboratory. Modification of the original method has made it possible to measure a difference in osmotic pressure of .004 per cent sodium chloride equivalent. This equipment is being employed currently to relate osmotic pressure of intra-ocular fluids to intra-ocular pressure and to determine the relative osmotic pressure of the aqueous humor in the posterior and anterior chambers of the eye.

The study of the variation of visual acuity as a function of movement of the object viewed has been continued by Dr. Elek Ludvigh. Experiments have been conducted at greater angular velocities and higher intensities than those previously employed. It is found that at high angular velocities of the object visual acuity is still significantly improving at an intensity of 2640 ft. candles.

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Experiments conducted by Dr. Ludvigh using black rectangular figures on a white background show that the visibility of such rectangles is dependent on their area and not on the lesser dimension of the rectangle, unless the ratio of greater to lesser dimension exceeds nine. This discovery has permitted the extension of the mathematical treatment of the theory of the visibility of moving objects to include those instances in which the object presents a variably oblique aspect to the observer.

An experimental technique is being developed for the optical measurement of fluorescent substances objectively in the eye. The use of highly stable voltage sources in conjunction with a multiplier phototube and negative feedback amplification with a parallel T resistance capacitance feedback impedance has so far permitted the detection of concentrations of .000004 per cent fluorescein in quantities of only 0.5 cc. When rabbits are injected intravenously with fluorescein which subsequently appears in and leaves the aqueous the measurement of aqueous fluorescence is interfered with by the normal fluorescence of the crystalline lens. The spectral composition of the light attributable to lens fluorescence is, however, different from that of fluorescein fluorescence, and a color flicker technique has been developed which promises to minimize this obstacle. It is hoped that this technique may be applied to human beings so as to ascertain the rate of flow of fluorescein into and out of the aqueous humor in different age groups and in normal and pathological conditions.

In a wide study of pharmacology of the eye, Dr. Grant has made a number of new observations which may be mentioned here and in the subsequent section on Clinical Sciences. Especially noteworthy is the comparative study of the anticholinesterases. A striking species difference was found for the guinea pig and man in the pupillary response to tetraethyl pyrophosphate and diisopropyl fluorophosphate, but in both species the former was the more active miotic. Observations have also been made on the inactivation of tetraethyl pyrophosphate by human vitreous. Several new anticholinesterase substances have been tested for their ocular effects. Parathion was found to have little miotic activity. Several anticholinesterase anthraquinone derivatives, furnished by Professor Louis Fieser of the

Harvard Chemistry Department, were tested but appeared not to have appropriate solubility properties for penetration into the eye from topical application.

In conjunction with Dr. Trotter, Dr. Grant is currently making an experimental comparison of various cholinergic miotic compounds based on characterization and measurement of their varied actions in animals and human beings on the pupil, ciliary muscle, vessel calibre and blood-aqueous barrier. Observations are also being made on corneal penetration properties and effects on non-ocular organs, e.g. salivary glands. Attempts have also been made to improve the synthetic preparation of 2268 F (Fourneau).

With the aim of finding a suitable vitreous substitute, a brief study has been made on the toxic effects of intravitreal injections of gelatin, silicones and proteases. The results were not promising.

In conjunction with Dr. Donald Loeb, Dr. Grant determined the relative toxicity to the eye of various antihistaminic drugs recommended for use in treatment of allergic diseases. No appreciable difference was found in those tested.

Attempts by Dr. Cogan to produce the experimental counterpart of band keratopathy have been unsuccessful. Acute hypercalcemia induced by estrogenic substances (in rabbits) and by parathormone (in dogs) has not resulted in visible calcification of the cornea such as is frequently found with hypercalcemia of human beings. Similarly experiments done in conjunction with Dr. Pierre Danis and aimed at producing precipitation of calcium salts beneath the epithelium of excised cat and beef corneas have been inconclusive.

Further observations have been made by Dr. Cogan in conjunction with Dr. Kinsey on the permeability of the cornea using radioactive sodium and radioactive Ray-o-pac. The results confirm the previous finding in showing that the surface membranes of the cornea provide an extraordinary barrier to non-corrosive, non-fat soluble substances. The permeability of the cornea to carbon dioxide and the exhalation of the cornea of carbon dioxide have been studied in conjunction with Dr. Danis and indicate that the corneal epithelium is freely permeable to carbon dioxide and under physiologic conditions, provides an avenue for considerable loss of this gas.

In view of the barrier properties of the surface membranes of the cornea to electrolytes as previously found in this Laboratory, one would not expect the cornea to be a suitable membrane for iontophoresis as the clinical evidence suggests it to be. To study this apparent paradox, Dr. Dyson made a study of iontophoresis for the excised beef cornea using cations, anions and non-electrolytes as test substances and found that iontophoresis applied to the cornea increased the transfer of substances not only by reason of their electric charge, but also by making the membrane itself more leaky.

CLINICAL SCIENCES

Preliminary observations by Dr. Kinsey and Dr. Zacharias on retrolental fibroplasia, a project supported by the Foundation for Vision, have indicated that the incidence of this disease bears a most suggestive relationship to the feeding of premature infants with vitamins in a water-miscible form. If these preliminary impressions are borne out by the more exhaustive analysis now being conducted and especially by the elimination of the disease by the discontinuance of these substances, a most important contribution will have been made to the pathogenesis of, and prevention of, blindness in infants.

Four additional cases have been studied of the disease entity known as "non-syphilitic interstitial keratitis with vestibulo-auditory symptoms" which was described by Dr. Cogan several years ago. Despite this study, the etiology remains almost totally obscure.

An attempt has been made by Dr. Cogan to correlate certain of the physiologic properties of the cornea with its manifestations in clinical disease especially as regards turgescence, bullous keratopathy and neovasculogenesis in the cornea. The chief features of this study were presented as the third Proctor Lecture in San Francisco and as the opening address of the German Ophthalmologic Society meeting in Heidelberg during the past year.

A clinical investigation with reference to glaucoma is being made on the action of tetraethyl pyrophosphate and other anti-cholinesterase drugs by Dr. Grant in conjunction with the experimental studies already noted. Tetraethyl pyrophosphate, which Dr. Grant introduced into ophthalmic practice, appears to compare favorably in pressure-lowering action, infrequency of pressure-raising action, comfort and supply (it is manufactured in quantity as an insecticide) but to have a disadvantage in frequency of local sensitization. The antiglaucoma efficacy of cholinergic agents other than the anticholinesterases is also being investigated. An interesting early development has been the experimental observation that a cyclic acetal analogue of the more familiar choline derivatives has a disproportionately large stimulatory effect on the ciliary muscle and that clinically this compound is unusually effective in lowering intra-ocular pressure.

A cursory survey was made by Dr. Grant of the relative efficacy of epinephrine and naphazoline (privine) in certain types of glaucoma, but the preliminary observations have led to no conclusive results.

Under the joint auspices of the Massachusetts Eye and Ear Infirmary and the Howe Laboratory, Dr. Schepens has organized the Retina Service to which all ward patients with detachment of the retina and related conditions are referred for study and treatment. The value of such an organization is already apparent both from the point of view of the individual patient and from a longer range point of view in the accumulation of data for statistical analysis, instruction of residents and for further research. As by-products of his interest in detachment of the retina, Dr. Schepens has developed more satisfactory methods of ophthalmoscopy and transillumination and improved the means by which optical instruments may be sterilized.

Several ophthalmic procedures such as campimetry and phoria measurements depend on visual fixation, and the exactness of this is usually controlled by gross inspection. To determine the accuracy that can be expected of these tests, Dr. Ludvigh has shown by experimental investigation that even under ideal conditions eye movements of less than 2^{Δ} cannot consistently be perceived by the unaided eye.

Of some interest and possible practical usefulness is the discovery by Drs. Cogan and Grant that a few applications of the common antiglaucomatous agent, ½ per cent physostigmine salicylate ointment, is an effective agent for the treatment of pediculosis ciliaris. Tetraethyl pyrophosphate and presumably other cholinergic compounds are also effective.

The camera for photography of the outer eye, developed by Drs. Trotter and Grant using an electronic flash illumination, has proved so satisfactory that attempts are now being made to devise an analogous means for taking pictures of the fundus and of the anterior chamber angle.

Teaching

The participation of the Howe Laboratory staff in teaching was considered at some length in last year's report, and no major change has occurred this year. The bulk of the teaching in the three months' course on basic sciences in ophthalmology continues to be done by the Laboratory staff, as well as some formal and much informal teaching elsewhere. A new adventure this year is the series of lectures and demonstrations by Drs. Ludvigh and Grant to a small class of prospective Orthoptic technicians. Dr. Cogan also gave a series of lectures on the cornea entitled "Principles of Corneal Disease" in Mexico City as the guest of the Sociedad Mexicana de Oftalmologia and a number of lectures on the physiology of the cornea, neuro-ophthalmology and ocular pathology at various university centers in Germany. These latter were part of the Medical Mission to Germany sponsored by the Unitarian Service Committee and is the first of such missions to include an ophthalmologist. Dr. Cogan also gave the third Proctor Lecture and held a teaching clinic in San Francisco this year.

Personnel

In recent years it has been the policy of the Howe Laboratory to have two main categories of personnel: those who were following a career of ophthalmic investigation and those who joined forces with the Laboratory for a period of a year or so as part of their training program or for work on some problem in co-operation with the Howe Laboratory staff. The former category includes Drs. Ludvigh, Kinsey, Grant and Cogan and has been relatively constant from year to year; the latter category included during the past year Dr. Ernest Bárány (Sweden), Dr. Charles Dyson (Canada), Dr. Charles Schepens (Boston), Dr.

Pierre Danis (Belgium), Dr. Robert Trotter (Boston) and Mr. Frederic Merriam* (Boston).

A new administrative code has now gone into effect for all departments of Harvard Medical School, which will necessitate profound changes in the foregoing setup as applied to the career staff unless some alternative plan is found. It is now decreed that departments having the budgetary size of the Howe Laboratory can have only one member of the department on a permanent basis and others cannot remain in the department more than a total of eleven years. How this is to be applied to departments which like the Howe Laboratory are fundamentally pure research departments and which have close affiliation with the hospital remains to be clarified.

Howe Library

The Howe Library, under the guidance of Miss Jeanette Loessl, continued its valuable services to the Infirmary, the Laboratory and a variety of extramural individuals and organizations in providing sources of reference and distribution of ophthalmic literature. The attendance at the Library for the past year was of the order of 5,500 visits.

Soliciting and sending American journals and some ophthalmic instruments abroad, both to Europe and Asia, has been pursued on a somewhat reduced scale. Owing to the generosity of the Year Book Publishers, Inc., several sets of *Ophthalmology in the War Years* have been made available for shipment to Europe.

At the suggestion of Dr. Parker Heath, an exhibit of ophthalmoscopic atlases was held at the combined annual meeting of the Eye and Ear Infirmary alumni and New England Ophthalmological Society. This proved highly interesting.

Because of the increasing use of the library for non-library functions, such as meetings and conferences, it has been necessary to post notices reminding users of the prime purposes of the library and the intention of the library administration to maintain these purposes.

Support of the Laboratory

Like most non-commercial organizations, the Howe Laboratory has been severely hurt by the inflation; the rise in costs of operation cannot be passed on to any product. The premium for research has not risen with the cost of maintenance. Nor can the main costs be passed on to the "project" money which has been so readily available of late and which has given the public the impression that there is an abundance of money for research. Project support is limited to specific and, for the most part, terminal investigations. It is neither expedient nor practicable to support a continuing or career-type of program on project money, although it is entirely possible to underwrite junior fellows or make temporary expansions on such a basis. To meet the shrinking purchasing power of the Laboratory's endowment, it would perhaps be proper to launch a money-raising campaign. Such has not been done to date chiefly because the time and effort necessary would devolve on the staff who are already pressed for time in their research and teaching activities.

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* Candidate for Ph.D. degree (Boston University).

It is all the more gratifying, therefore, to record the donations from organizations and from individuals which, for the most part, were entirely unsolicited. These donors have shown their appreciation of the goals set by the Laboratory and have made contributions for the continuation of its activities. Those of us who are close to the operation of the Laboratory feel that it is one of the most worthy and fruitful charities. In the name of those who in the past year or in the future may profit from the investigations of the Howe Laboratory, a vote of gratitude is in order for the following generous and understanding benefactors:

The Massachusetts Eye and Ear Infirmary, for general expenses.
American Optical Company, for the support of research in physiologic optics (third year of a three-year grant).
The Eye-Bank for Sight Restoration, Inc., New York City, for studies on the cornea and lens.
The Snyder Foundation, for determination of relative osmotic pressure in blood and aqueous humor.
Paul A. Chandler, M.D., for general expenses.
Thomas R. Gaines, M.D., for general expenses.
Benjamin Sachs, M.D., for general expenses.
Earle S. Seale, M.D., for general expenses.
Mr. William N. Stevenson, for general expenses.
Board of Surgeons in Ophthalmology, for operating expenses of the Library.

David G. Cogan, M.D.
Director

LECTURES WHICH WERE GIVEN AND ARTICLES WHICH WERE PUBLISHED DURING 1948

Bárány, E. Reciprocal inhibition between the two retina. Presented at the Psycho-Acoustic Laboratory, Harvard University, in Cambridge, Massachusetts, May, 1948.

Bárány, E. Circulation of the eye and intra-ocular pressure. Presented at the Department of Physiology, Harvard Medical School, in Boston, Massachusetts, May, 1948.

Cogan, D. G. Pediatric Ophthalmology. Section XVI in *The Child in Health and Disease*. Grulee, C. R. and Eley, R. C., Baltimore, Williams & Wilkins Co., 1948.

Cogan, D. G. *Neurology of the Ocular Muscles*. Springfield, Illinois, Thomas, 1948, vii, 214 pp.

Cogan, D. G. Neurologic significance of lateral conjugate deviation of the eyes on forced closure of the lids. Arch. Ophth. 39: 37–42, January, 1948.

Cogan, D. G. Students' model for demonstration of action of the extraocular muscles. Arch. Ophth. 39: 92–93, January, 1948.

Cogan, D. G. Principles of corneal disease. Series of lectures to Sociedad Mexicana de Oftalmologia, in Mexico City, Mexico, February, 1948.

Cogan, D. G. Physiologie der Cornea. Hyperkalcemie und bandformige Keratopathie. German lectures presented at the German Ophthalmological Society, in Heidelberg, Germany, August, 1948.

Cogan, D. G. The relationship of corneal turgescence, epithelial edema, bullous keratopathy and interstitial vascularization. The third Proctor Lecture presented at the University of California Medical School in San Francisco, California, September, 1948.

Cogan, D. G. Dynamics of corneal vascularization. Presented at the New England Ophthalmological Society, in Boston, Massachusetts, November 16, 1948.

Grant, W. M. and Cogan, D. G. Biochemistry, pharmacology, toxicology (of the eye). In *Ophthalmology in the War Years*, Vol. II, (1944–June, 1946). M. Wiener, Ed., Chicago, the Year Book Publishers, Inc., 1948, pp. 20–62.

Grant, W. M. Colorimetric microdetermination of formic acid based on reduction to formaldehyde. Anal. Chem. 20: 267–269, March, 1948.

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Kinsey, V. E. Spectral transmission of the eye to ultraviolet radiations. Arch. Ophth. 39: 508–513, April, 1948.

Kinsey, V. E. Radioactive isotopes in medicine. Presented at the Chelsea Naval Hospital, Chelsea, Massachusetts, May 4, 1948.

Kinsey, V. E. and Bárány, E. Rate of flow of aqueous humor. 2. Derivation of the rate of flow and its physiologic significance. Presented by Dr. V. Everett Kinsey at the Association for Research in Ophthalmology, in Chicago, Illinois, June 22, 1948.

Kinsey, V. E. (in collaboration with Mrs. Eunice Wilson). Retrolental fibroplasia. For parents of children who have this ocular disease. Boston, Massachusetts Eye and Ear Infirmary, [1948], 7 pp.

Kinsey, V. E. Recent concepts in aqeous humor dynamics. Presented at the Association for Research in Ophthalmology, in New York City, New York, November 13, 1948.

Kinsey, V. E. and Zacharias, L. The incidence of retrolental fibroplasia in different localities and a correlation of the incidence with treatment given the infants. Presented by Dr. V. Everett Kinsey at the Alumni Meeting of the Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, November 17, 1948.

Ludvigh, E. J. An hypothesis concerning amblyopia ex anopsia. Presented at the New England Ophthalmological Society, in Boston, Massachusetts, February 18, 1948.

Ludvigh, E. J. The visibility of moving objects. Science 108: 63–64, July 16, 1948.

Schepens, C. L. and Bahn, G. C. Examination of the ora serrata. Presented by Dr. Gustav C. Bahn at the New England Ophthalmological Society, in Boston, Massachusetts, March 17, 1948.

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Trotter, R. R. and Grant, W. M. The electronic flash (gas discharge tube) in anterior segment photography of the eye. Arch. Ophth. 40: 493–496, November, 1948.

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Ludvigh, E. J. An investigation of the amount of practice advisable in ranging on a simulated-diving-aeroplane target, 1942. Pub. Bd. No. 55793, Washington, D. C., U. S. Department of Commerce, 1947, 14 pp.

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Ludvigh, E. J. Progress Report. [Accuracy of stereopsis as a function of the first and second derivatives of disparateness with respect to time], n. d. Pub. Bd. No. 55792, Washington, D. C., U. S. Department of Commerce, 1947, 5 pp.